## REMARKS

By this amendment and solely to expedite allowance, Applicant has amended claims 1, and 12 to include that the method, among other things, determining the pH, sialidase level and/or prolidase activity in samples of cervo-vaginal fluid. Claims 5, 7, 8, 9, 10, have also been amended to include that the sample is cervo-vaginal fluid. Support for this amendment can be found in the specification and claims as filed, for example, page 26, line 24 to page 28, line 15 and page 30, lines 10-12 and Table 1 and 2. No new matter has been added. Claim 5 has been amended to remove reference to "malignancies of the urogenital tract" and replace it with cervical cancer. Support can be found, for example, on page 2, lines 1-16. No new matter has been added.

Applicant has also added new claim 28, which includes, among other things, the step of providing a value indicative of the risk of developing certain pathologies. Support can be found in the specification, for example, Table 1, values in bold and in detail, step i): page 9, lines 3-4 and 8-9; step ii) at page 9, paragraph 23; step iii) page 11, lines 17-18 and page 9, lines 1-3; step iv) page 12, lines 13-17. No new matter has been added.

Applicant has also canceled claim 4, without disclaimer and reserve the right to pursue this claim in one or more continuing/divisional applications. All rejections are moot with regard to canceled claim 4. Applicant respectfully requests entry of the amendments and allowance of the case.

**Provisional Obviousness-type Double Patenting**

The Examiner provisionally rejects claims 1-16 based on co-pending Application No. 10/467,357. Applicant respectfully disagrees with the Examiner, however, Applicant, if necessary, will file a terminal disclaimer once allowable subject matter is indicated.

**Rejection Under 35 U.S.C. § 103(a)**

Claims 1-16 are rejected by the Examiner as allegedly being obvious under 35 U.S.C. §103 in light of Soothill, Johnson, Lawrence, Cauci, Cauci, McGregor and Briselden. Applicant respectfully traverses this rejection.

The problem solved in various embodiments of the present invention is to provide a method which allows quantifying the risk of contracting pathologies caused by infections of bacteria producing the sialidase or prolidase enzyme. The method provides a reliable value of the risk so that the clinician now has a new tool in deciding whether or not to administer, for example, a pharmacological therapy, which may have several drawbacks (see page 5, paragraph 8). In various embodiments, the present invention solves the problem of identify those women who have a risk of contracting obstetric or gynecologic complications and those who can develop the complications in an early gestation period (see page 7, paragraphs 13 and 14). The Examiner should bear in mind that the method is independent from the detection of the bacterial vaginosis (BV), so that the method can be more accurate and does not depend on the subjective determination of BV by the clinicians or have to take into account that there could be false negative detections. Keeping the above in mind, Applicant submits that none of the prior art references cited by the Examiner disclose, teach or suggest the claimed methods. In particular, the cited prior art differs from the claims since they do not disclose the steps of selecting samples having particular sialidase, prolidase and pH levels.

With regard to new claim 28, the prior art does not disclose, teach or suggest step b) providing a value indicative of the risk which value is obtainable as specified in steps i) to iv). Applicant respectfully submits that the present application is new over the prior art documents.

In various embodiments, the problems solved by the present invention is to provide a method which allows quantifying the risk of contracting pathologies caused by infections of bacteria producing sialidase or prolidase enzyme, and to allow the selection of a particular population of women having a very high risk of contracting obstetric and gynecologic diseases and to allow such determination in an early gestation period. In contrast, the prior art cited by the Examiner solves completely different problems.

In particular, McGregor, which appears to be the closest prior art, solves the problem of gaining insight into how bacterial vaginosis or associated microorganisms and vaginal fluid enzymes may play roles in the pathogenesis of preterm birth by prospectively studying women with or without bacterial vaginosis during pregnancy (see

page 1049, second paragraph of right column). Moreover, McGregor solves the problem of seeing whether pregnancy outcomes could be improved by analyzing pregnancy results and changes in vaginal fluid mucinase and sialidase after treatment with 2% clindamycin vaginal cream for bacterial vaginosis (see page 1049, second paragraph of right column and Table IV). McGregor solves the problem by the comparison between women with and without bacterial vaginosis, these last after having been treated with clindamycin (see Table IV and right column of page 1054). It is evident that the relative risk of pregnancy outcomes calculated in Table IV is derived from a correlation between patients with bacterial vaginosis compared with those without bacterial vaginosis.

In contrast, the presently claimed invention, as already stated, is independent from the presence of bacterial vaginosis and, moreover, it is performed on the evaluation of sialidase and/or prolidase enzyme and the calculation of the risk factor of obstetric and/or gynecologic pathologies on the basis of the provision of a value indicative of the risk of obtaining the claimed pathologies. Therefore, one of ordinary skill in the art would have never taken into consideration McGregor when facing the problems solved by the present invention. Moreover, even if the skilled artisan reviewed McGregor, he would only recognize that there exists a correlation between a specific inflammatory status, i.e. bacterial vaginosis, and some adverse pregnancy outcomes. Accordingly, there are no suggestions in McGregor on how to quantity the risk of pathologies related to the presence of bacteria producing sialidase and/or prolidase enzyme as claimed in the subject application independently from the presence of bacterial vaginosis.

In addition, McGregor teaches to calculate the relative risk considering patients who received a 2% clindamycin vaginal cream treatment (see second column of Table IV). It is evident that the value of said relative risk is heavily conditioned by said treatment.

On the contrary, the value indicative of the risk provided following the method of the present invention is not altered by any treatment. Therefore, the value indicative of the relative risk of McGregor can be dramatically different from the risk factor that is calculated according to the subject application. Furthermore, McGregor does not take into account the false negative, i.e. patients who do not show typical bacterial vaginosis

symptoms but who could have a high risk. It is also noted that McGregor does not teach or suggest a method for selecting a particular population of women having a very high risk of obstetric and/or gynecologic outcomes. In fact, said selections come from the surprising and unexpected correlation between those particular enzyme values of sialidase and prolidase and pH. In particular, the Applicant has found that only taking into consideration this peculiar selection of values, it is possible to determine among all the women those who have a risk of obstetric and/or gynecologic complications higher that the threshold of 5.5 (OR value) which is considered as the actual dramatic threshold for said complications. Therefore, this value, and thus the corresponding method can be of paramount importance for the physicians in order to evaluate if it can be convenient to administrate antibiotics or not in the light of their well-known and dangerous side effects. In view of the above, it is submitted that the skilled artisan would have never reached the solution adopted in the subject application, when facing the above technical problem, through the reading of McGregor.

With regard to Briselden, this reference investigates vaginal fluid for sialidase activity and compares levels of said sialidase activity in the vaginal fluid of women with BV with those detected in the vaginal fluid collected from women characterized as not having BV (see page 663, second paragraph of right column). In particular, sialidase activity in vaginal fluid of women with BV and of women without BV (Figure 1) has been detected. On the contrary, as stated above, the subject application solves a different problem, i.e. providing a method for determining the risk of pathologies related to the presence of bacteria producing sialidase and/or prolidase enzyme independently from the bacterial vaginosis status. Therefore, the skilled artisan would have only learned from Briselden that the presence of higher level of sialidase enzyme is a marker for bacterial vaginosis. However, no reference is made on how to determine the risk factor or at least a value indicative of the risk of said pathologies.

Applicant also notes that from page 665, last sentence to page 666, where Briselden states that further studies are needed to determine whether there is a relationship between sialidase activity in vaginal fluid and prematurity, upper genital tract infection, and BV and, more important, that it will be of interest to determine whether

sialidase in the vaginal fluid of pregnant women are associated with increase risk of preterm labor or invasion of amniotic cavity. Therefore, it is clear that Briselden does not disclose, teach or suggest the present claims. In addition, once again, Briselden discloses a strict correlation between BV and sialidase activity but does not suggest how to calculate a risk factor independently from BV.

With regard to Soothill (WO00/55354), Lawrence (5,571,684), and Johnson (WO0024753), Applicant notes that they deal with different methods.

Soothill discloses a diagnostic test for diseases such as BV, which detects presence of sialidase activity. No reference to a method for the determination of the risk of pathologies related to the presence of bacteria producing sialidase and/or prolidase is made.

Lawrence discloses a method for detecting proline aminopeptidase activity. No reference to a method for the determination of the risk of pathologies related to the presence of bacteria producing sialidase and/or prolidase is made.

Johnson discloses a method of diagnosis of sialidase related disease using a particular substrate compound. No reference to a method for the determination of the risk of pathologies related to the presence of bacteria producing sialidase and/or prolidase is made.

Therefore, Applicant respectfully submits that through the reading of any one of the above prior art references and having in mind the objective technical problem faced by the subject application, the skilled artisan would have never reached the solution claimed in the subject application.

With reference to Cauci et al. (Am J. Obstet Gynecol), Applicant notes that it relates to a study to investigate the correlation between the immunoglobulin A immune response to *G. vaginalis* hemolysin and sialidase activity in vaginal fluids from patients with bacterial vaginosis. The whole study design concerns non-pregnant women, thus it is evident that said study cannot teach or suggest how to predict a risk of obstetric and/or gynecologic complications in general and, in particular to those patients being in the early gestation period.

With regard to Cauci (J. of Infect Disease), Applicant notes that it also deals with

non-pregnant women, thus the same consideration as above must be made. In addition, both the above Cauci references again do not provide a specific selection of enzymatic and pH values which allow surprisingly and unpredictably to detect those women who have actually a very high risk of suffering from serious obstetric and/or gynecologic complications.

In summary, none of the cited references, alone or in combination, disclose, teach or suggest the present claims. Nor do they solve the problem recognized by the present claims. Thus, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

**Rejection under 35 U.S.C. §112, First Paragraph**

The Examiner rejected claims 1-16 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. Applicants have amended the claims to include determining a women's risk of developing the claimed pathologies by, among other things, determining the pH, sialidase level and/or prolidase activity in samples of cervo-vaginal fluid. Applicant submits that the specification enables one of ordinary skill in the art to practice the claimed invention.

In particular, claims 1 and 12 have been amended deleting the references to the methods of determining enzymatic activities as described in Cauci references. Applicant also notes that said references disclose methods to determine the sialidase and prolidase activities, respectively, as non-limiting examples. In fact, from page 26, line 24 to page 28, line 15 two different processes for each determination have been disclosed in the present application. However, the same are to be considered as examples of methods well known to the skilled artisan. This can be also understood through the passage of page 30, lines 10-12 wherein it is stated that the enzymatic activity are calculated for example with the above identified procedures.

In addition, the reference to the "body fluid" in general has been substituted with cervo-vaginal fluid, thus reducing the kind of fluids to those clearly described as derivable from the application as filed and in particular to the examples. For example, it is well known that for anatomic reasons the body fluids of the cervical and vaginal

tracts are not easily separable so that a contamination between them can occur. Applicant also directs the Examiner to the large quantity of data supporting enablement shown, for example, in Tables 1 and 2 and corresponding description where it has been unambiguously demonstrated that the method of the invention works with unexpected results when performed on the above fluids.

With regard to amended claim 5, the phrase "malignancies of the urogenital tract" has been removed and substituted with "cervical cancer". Therefore, all the other urogenital tract malignancies have been deleted from consideration so that the Examiner's objections on this point are moot.

Moreover, the amendment to "cervical cancer" is clear to one of ordinary skill in the art on reading the specification since it is well known that the viruses disclosed in the specification, and in particular HPV, are responsible for cervical cancer. All the other pathologies and infections reported in claim 5 are well known to derive from BV infections cause by *G. vaginalis* and other infections caused by those micro-organism disclosed at page 2, lines 1-4 of the description.

In further support of the enablement, some more recent references (abstracts) are enclosed in order to demonstrate the actual relevance of the method of the present invention for the diseases disclosed.

- Myer I. et al "Intravaginal practices, bacterial vaginosis, and women's susceptibility to HIV Infection: epidemiological evidence and biological mechanisms. Lancet Infect Dis. 2005 Dec: 5(12) 786-94.
- Myer et al "Bacterial vaginosis and susceptibility to HIV infection in South African women: a nested case-control study. J. Infect Dis. 2005 Oct. 15; 192(8): 1315-7
- Schwebke Jr. Abnormal vaginal flora as a biological risk factor for acquisition of HIV infection and sexually transmitted diseases. J. Infect Dis. 2005 Oct. 15: 192(8):1315-7. Epub 2005 Sep. 9
- Hay PE. Bacterial vaginosis and miscarriage. Curr Opin Infect: Dis. 2004 Feb: 17(1) 41-4

- Wisenfeld HC, et al "Lower genital infection and endometritis: insight into subclinical pelvic inflammatory disease. Obstet Gynecol, 2002 Sep: 100(3):456-63
- Wilson JD et al "Rates of bacterial vaginosis in women undergoing in vitro fertilization for different types of infertility". BJOG 2002 June:109(6) 714-7

Also, analogous considerations can be made through the reading of the same prior art cited by the Examiner. Accordingly, Applicant submits that the subject application does not cause an undue quantity of experimentation or an insufficient direction or guidance for carrying out the claimed invention. In fact, as stated above, the body fluid has been specified as been cervo-vaginal fluid upon which the method is performed, the diseases disclosed are all well known to be correlated to the presence of BV status, as also available from the same prior art cited by the Examiner, and related micro-organisms.

In addition, it is to be noticed that the examples support and enable applicability for pathologies having the same etiology, such as low birth weight (LBW), very low birth weight (VLBW) preterm delivery (PTD), early preterm delivery (EPTD), premature rupture of membranes, preterm premature rupture of membranes, intraamniotic infections, spontaneous abortion, endometritis, obstetric surgery infections, post-partum or post-gynecologic surgery infections, pelvic surgery infections, upper genital tract infections which cause infertility, pelvic inflammatory disease (PID), annexitis, cervicitis on one hand and sexually transmitted diseases and infections and cervical cancer on the other hand.

It is respectfully submitted that the specification fully complies with the enablement requirement for claimed methods. Accordingly, Applicant respectfully requests withdrawal of this rejection.

**Rejection under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected claims 1-16 as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicant regards as the invention.

Applicant has amended the claims to positively recite the method steps and submits that the claims are definite to one of ordinary skill in the art. Accordingly. Applicant requests reconsideration and withdrawal of the rejections based on 35 U.S.C. §112, second paragraph.

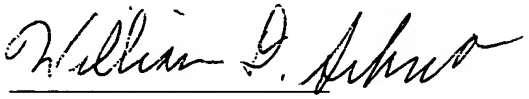
**Conclusion**

Reconsideration and allowance are respectfully solicited.

Applicant petitions for a 3-month extension of time and encloses the required fee. No additional fee is believed to be due with respect to the filing of this amendment. If any additional fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,



William D. Schmidt
Registration No.: 39,492
Attorney for Applicant

Kalow & Springut LLP
Telephone: (212) 813-1600
Facsimile: (212) 813-9600